IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Conf. No. 2806.
	)	
Wingard *et al.*	)	Group Art Unit: 1612
	)	
Serial No.: 10/509,627	)	Examiner: Sutton Darryl C
	)	
Filed: April 29, 2005	)	Docket No. 006050.00067

For: Pharmaceutical Compositions Containing Water-Soluble Prodrugs Of Propofol And Methods Of Administering The Same

RESPONSE TO NOTIFICATION OF NON-COMPLIANT APPEAL BRIEF

401 Dulany Street
Alexandria, VA 22314

Sir:

In response to the Notification of Non-Compliant Appeal Brief dated December 24, 2009, Appellants submit herewith an amended appeal brief. The Notification asserts that the summary of claimed subject matter section does not map independent claim 37 to the specification. In the accompanying corrected brief, the summary of claimed subject matter section is amended to map independent claim 37 to the specification.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Date: January 12, 2010
Customer No. 22907

By: /Paul M. Rivard/
Paul M. Rivard
Registration No. 43,446

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Brief on Appeal

Pursuant to 37 C.F.R § 41.37, Appellants submit this Appeal Brief to the Board of Patent Appeals and Interference in response to the Final Office Action mailed June 10, 2009. A Notice of Appeal was timely filed on September 10, 2009.

General Authorization of Payment of Fees

If any fees are due in this application, whether or not associated with this filing, please charge any fees due to Deposit Account No. 19-0733.

TABLE OF CONTENTS

I. Real Party in Interest

The owner of this application, and the real party in interest, is Eisai Inc.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of Claims

Claims 12, 13, and 36-39 are pending and stand rejected. Claims 14-19 are withdrawn. Claims 1-11, and 20-35 are canceled.

Appellants hereby appeal the rejection of claims 12, 13, and 36-39.

IV. Status of Amendments

No after final amendment or after final response was filed prior to the filing of the Notice of Appeal and this Appeal Brief.

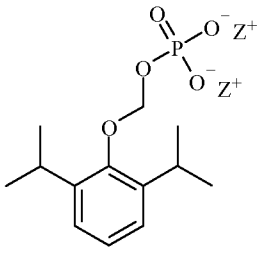
V. Summary of Claimed Subject Matter

Injectable anesthetic agents have gained widespread acceptance in anesthetic care over the last 15 years. (Specification ¶ 04). Propofol is a low molecular weight phenol derivative that is widely used as an injectable sedative agent for general anesthesia. (Specification ¶ 03). Propofol can also be used for conscious sedation; *i.e.*, local and regional anesthesia in conscious patients. Conscious sedation is useful, for example, during diagnostic procedures such as a

colonoscopy. (Specification ¶ 09). Propofol became popular due to rapid onset and offset of anesthesia, rapid clearance, and a better side-effect profile than other injectable anesthetics. (Specification ¶ 03). Because of its poor water solubility, propofol is formulated in a lipid emulsion for administering to patients. The lipid emulsion has a limited shelf-life and can become contaminated, leading to post-surgical infection. (Specification ¶ 06). The emulsion formulation is also sensitive to changes in droplet size and changes can cause undesirable side effects such as lung embolisms. Using propofol is further complicated by side effects such as apnea and hypotension, and pain on injection. Hypotension caused by rapid bolus injection of propofol limits the procedures that can use propofol bolus administration. (Specification ¶ 08). Longer sedation using propofol is administered by infusion is complicated by the development of hyperlipidemia due to the lipid emulsion formulation. (Specification ¶ 10). Fospropofol, which has a phosphonooxymethyl ether group in place of the 1-hydroxy-group, is more water soluble than propofol. (Specification ¶ 11).

Independent claim 12 is directed to a method of producing conscious sedation in a human by parenteral administration of a bolus containing about 2 mg/kg to less than 15 mg/kg of a propofol prodrug of Formula I as a phosphate or an akali metal ion salt, where Formula I is:

Formula I



wherein each Z is independently selected from the group consisting of hydrogen and alkali metal ion.

Single bolus doses of the prodrug were found to cause loss of consciousness with substantially the same rapidity as an equipotent rapid infusion of propofol and result in a relatively longer duration of unconsciousness. (Specification ¶ 49). The prodrug can be administrated without pain as a bolus and was associated with less frequent occurrences of apnea and other side effects. (Specification ¶ 49). Thus, the claimed method permits parenteral bolus administration of the prodrug without the side effects caused by infusion of propofol emulsion, while effectively providing conscious sedation.

Claim 13 depends from claim 12 and specifies that the compound is administered in an amount of 5 to 10 mg/kg.

Independent claim 37 is directed to producing conscious sedation in a human by parenteral administration of a bolus containing about 5 mg/kg to about 10 mg/kg of a propofol prodrug of Formula I as an alkali metal ion salt. (Specification ¶ 31).

Dependent claims 36 and 38 recite a dosage of from about 5 mg/kg to about 7.5 mg/kg.

VI. Grounds of Rejection to be Reviewed on Appeal

Claims 12, 13, and 36-39 stand rejected under 35 U.S.C. § 103(a) over Stella (U.S. Pat. No. 6,204,257)("Stella") in view of Lowrie *et al.* ("The pediatric sedation unit: a mechanism for pediatric sedation," Pediatrics. 1998 Sep;102(3):E30)("Lowrie").

VII. Argument

A. The § 103 Rejection Should Be Reversed Because The Prior Art Fails to Provide a Reasonable Expectation of Success in Administering the Prodrug as a Bolus to Produce Conscious Sedation.

An obviousness rejection under 35 U.S.C. § 103(a) requires that the differences between the claimed invention and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614, 1616 (Fed. Cir. 1999); 35 U.S.C. § 103(a). The ultimate determination of obviousness is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) any objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399, 127 S. Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007), the Supreme Court explained, "While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls." The Court also said that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.*

The *KSR* Court relied heavily on predictability and specifically distinguished its earlier decision in *United States v. Adams*, 383 U.S. 39 (1966), where unexpected results led to a holding of non-obviousness. In *Adams*, the Court considered the obviousness of a wet battery that differed from the prior art in two respects. First, it contained water, rather than acids as conventionally used in storage batteries. Second, the electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The invention was held to be non-obvious, despite

the battery involving the substitution of elements that were known in the art. The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art. *KSR*, 127 S. Ct. at 1740.

As in *Adams*, the method of independent claim 12 is non-obvious at least because persons skilled in the art would not have had a reasonable expectation of success that administering a compound of Formula I in at least one parenteral bolus injection in an amount of from about 2 mg/kg to less than 15 mg/kg, would be effective for producing a conscious sedated state in a human subject.

Stella describes preparation of the prodrug fospropofol and its administration through different routes and in different doses. The doses described in Stella include 0.5 mg/kg to 10 mg/kg and 2 μg/kg/min to 800 μg/kg/min. Lowrie describes administering a bolus injection of propofol parenterally, but does not describe fospropofol. Lowrie does not describe a bolus injection of about 2 mg/kg to less than 15 mg/kg as recited in claim 12.

The Final Office Action acknowledges Stella does not teach a bolus parenteral injection in the claimed range but contends it would have been within the purview of one skilled in the art to produce sedation, i.e. anesthesia ranging from conscious sedation to a deep sedated state. Office Action of June 10, 2009 at page 6. But the mere fact something is possible does not establish obviousness. *Ex parte Levengood*, 28 U.S.P.Q. 2d 1300 (B.P.A.I. 1993). A *prima facie* case of obviousness requires some objective reason to combine the teachings of the references and, under *KSR*, the Supreme Court requires that a rationale explaining the reason is made explicit. *KSR Int'l Co.,* 550 U.S. at 401. Other than the capability of producing sedation, however, the Final Office Action has not articulated any reason why a skilled artisan would administer the prodrug in a bolus form in the recited dose. That a drug is capable of producing

sedation is not a reason to select a particular route of administration, let alone select bolus administration as the route or select the recited dose.

In fact, the Final Office Action recognizes that "[o]ne of ordinary skill would be [led] away from administering the compound, i.e. propofol, of Lowrie in higher bolus doses." *Id.* Nevertheless, the Final Office Action asserts that the artisan would not have been led away from administering the prodrug in a bolus because Stella teaches parenteral administration of the prodrug at 0.5 to 10 mg/kg and because Stella does not teach administration over a specific period of time. *Id.* This argument is flawed, however, because it assumes without support that a skilled artisan reading Stella would administer the amounts to a human as a *bolus* in the upper part of the disclosed range. Nothing in Stella indicates a preference for administration via bolus or rapid infusion over longer infusion.

Because propofol is produced directly from the prodrug by the action of alkaline phosphatase, and further because propofol was known to cause problems such as cardiorespiratory depression from bolus dosing, one of skill in the art would not have been led to administer the prodrug as a bolus. Propofol is administered to humans as a continuous infusion precisely to avoid these side effects. Thus, because one of ordinary skill in the art would not administer elevated amounts of propofol to humans in a bolus, one of ordinary skill in the art likewise would not have administered elevated amounts of the prodrug to a human in a bolus. The cited art contains no teaching or suggestion that the prodrug could or should be parenterally administered as a bolus in doses higher than those taught in Lowrie.

Further, the skilled artisan could not have predicted the difference in the propofol concentration profiles that would result from administration of propofol emulsion *versus* propofol prodrug. One of ordinary skill could not have predicted methods of achieving

conscious sedation based on the prior art data. In the response filed March 16, 2009, Applicants provided a Declaration of Dr. Ajit Shah. Dr. Shah discussed pharmacology studies that found "significant differences in plasma concentration-time profile" between propofol and the fospropofol prodrug. (Shah Dec. ¶ 6). Dr. Shah concluded that "[b]ecause of these differences, methods of administering fospropofol disodium for achieving conscious sedation could not have be[en] predicted from data based on propofol." Shah Dec. ¶ 6. Dr. Shah supported his conclusion by referring to data in Declaration Figures 6, 7, and 11. Figure 6 shows that propofol concentration in the plasma from fospropofol had a lower maximum propofol concentration than that from propofol emulsion injection and that the maximum occurred at a later time. Shah Dec. ¶ 5. Figure 7 showed that subjects receiving propofol experienced deeper sedation than those receiving fospropofol, that recovery from fospropofol-induced sedation was more gradual than from propofol injection, and that fospropofol provides a more sustained effect. Figure 11 shows that fospropofol produces a slower time to maximal effect and a more gradual recovery. Shah Dec. ¶ 7.

The Final Office Action asserts that the results are not unexpected and dismissed Dr Shah's conclusion. The Final Office Action dismisses the higher maximum obtained by propofol as expected based on metabolism of fospropofol disodium. But this is mere speculation. No support is supplied to explain the assertion that the fospropofol might undergo additional modifications. In fact, a skilled artisan might equally expect that because propofol is administered as an emulsion, extracting propofol from the emulsion would delay introduction of propofol into the bloodstream and delay sedation relative to an aqueous administration such as the prodrug. No rationale has been supplied to support the assumption that propofol availability from the lipid emulsion formulation allows predicting propofol availability from an aqueous

prodrug formulation. Moreover, Dr. Shah, who has worked in the pharmacokinetic field for at least 20 years, declared that data from propofol studies is insufficient to predict methods for administering the prodrug to achieve conscious sedation.

Furthermore, Applicants supplied a copy of the Diprivan® product insert, which establishes the skilled artisan would have been taught away from administering fospropofol as a bolus because propofol—the active drug produced from fospropofol—should not be administered as a bolus: "A rapid bolus injection [of propofol] can result in undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or oxygen desaturation." Diprivan® Product Insert at page 9 ¶ 2. The Final Office Action's dismissal of this teaching away as based on propofol rather than the claimed compound misses the point. One of ordinary skill in the art would have recognized that propofol is derived from fospropofol and would therefore have been concerned that fospropofol administration would result in a bolus propofol administration with its potentially dangerous consequences. It is this possibility that directs the skilled artisan away from administering fospropofol to humans as a bolus.

B. Claims 13, 37, and 39 Further Distinguish the Cited Art By Requiring a Dosage From About 5 mg/kg to About 10 mg/kg.

The Final Office Action asserts a teaching that 5 mg/kg and 10 mg/kg are effective does not support effectiveness of amounts between 2 mg/kg to less than 15 mg/kg. But no reasoning is provided to support this assertion. The Final Office Action also asserts that administering the compound as an alkali salt is not the same as administering a compound in its acid form. No reasoning is provided to support this assertion or explain its significance. Moreover, the salt moiety is part of the phosphonooxymethyl group that is cleaved from the prodrug and releases

the active drug. Therefore, because the phosphonooxymethyl/salt moiety is cleaved from the prodrug, differences between salt types are unlikely.

In any event, claims 13, 37, and 39 require a dosage of about 5 to 10 mg/kg, which further distinguishes the cited references and makes moot the Final Office Action's contention regarding the broader dosage range.

The Final Office Action's contention regarding the alleged distinction between an alkali metal salt and acid is moot with respect to claim 37, which requires an alkali metal salt, and claim 39, which requires the sodium salt.

In Example 3, Appellants demonstrate 5 mg/kg and 10 mg/kg amounts result in a sedated state and not loss of consciousness. Appellants' data was prepared with fospropofol disodium, an alkali metal salt of Formula I. Moreover, as the Shah Declaration shows, bolus administration to humans provides slower time to have a peak effect, a lower peak effect, but a more sustained sedative effect. Dr. Shah concludes that methods of administering fospropofol disodium for achieving conscious sedation could not have been predicted from data based on propofol.

C. Dependent Claims 36 and 38 Further Distinguish the Cited Art By Requiring a Dosage From About 5 mg/kg to About 7.5 mg/kg.

Dependent claims 36 and 38 recite a narrower dosage range of about 5 mg/kg to about 7.5 mg/kg. The arguments in Sections A and B above apply with equal force to claims 36 and 38.

In addition, claims 36 and 38 specify a narrower dosage range of about 5 mg/kg to about 7.5 mg/kg. There is certainly nothing in Stella or Lowrie, whether taken individually or in combination, that would have led the skilled worker to this particular dosage range for a bolus injection. The only basis for reaching such a conclusion is the hindsight gleaned by reading the

present specification, which is not a proper basis for an obviousness rejection. See M.P.E.P. § 2142 ("impermissible hindsight must be avoided and the legal conclusion [of obviousness] must be reached on the basis of facts gleaned from the prior art.").

CONCLUSION

For the foregoing reasons, the § 103 rejection should be reversed.

Respectfully submitted,

Date: January 12, 2010

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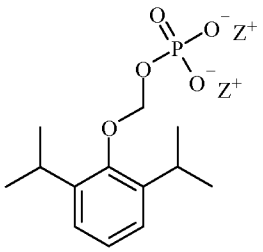
VIII. CLAIMS APPENDIX

1-11. (canceled)

12. (rejected) A method of producing a conscious sedated state in a human subject comprising administering to a human subject in need thereof a compound of Formula I:

Formula I



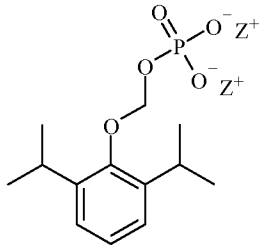
or a pharmaceutically acceptable salt thereof, wherein each Z is independently selected from the group consisting of hydrogen and alkali metal ion;

wherein the conscious sedated state is produced in the human subject by administering to the human subject at least one parenteral bolus injection in an amount of from about 2 mg/kg to less than 15 mg/kg.

13. (rejected) The method of claim 12, wherein the compound is administered in an amount of from about 5 mg/kg to about 10 mg/kg.

14. (withdrawn) A method of inducing and maintaining a conscious sedated state in a subject comprising administering to a human subject in need thereof a compound of Formula I:

Formula I



or a pharmaceutically acceptable salt thereof, wherein each Z is independently selected from the group consisting of hydrogen and alkali metal ion, wherein a conscious sedated state is produced by administering to the human subject at least one bolus injection in a first amount sufficient to induce the conscious sedated state; and

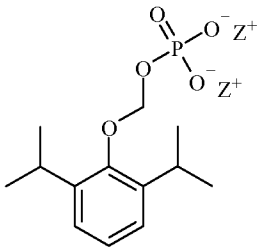
administering, once or repeatedly, to said human subject a compound of Formula I, or a pharmaceutically acceptable salt thereof, in a second amount sufficient to maintain the conscious sedated state.

15. (withdrawn) The method of claim 14 wherein the first amount is administered by a bolus injection at a dose of from about 5 to about 15 mg per kilogram of body weight, and the second amount is administered by a bolus injection at a dose of from about 2 to about 10 mg per kilogram of body weight.

16. (withdrawn) The method of claim 14 wherein the first amount is administered by a parenteral infusion at a rate of from about 5 mg/min. to about 25 mg/min., and the second amount is administered by a parenteral infusion at a rate of from about 5 to about 15 mg/min.

17. (withdrawn) A method of producing a conscious sedated state in a human subject comprising administering to a human subject in need thereof a parenteral infusion of a compound of Formula I:

Formula I



or a pharmaceutically acceptable salt thereof, wherein each Z is independently selected from the group consisting of hydrogen and alkali metal ion;

wherein the compound is administered in an amount of from about 5 to about 25 mg/min to produce the conscious sedated state in the human subject.

18. (withdrawn) The method of claim 17 wherein the compound is administered in an amount of from about 7 to about 20 mg/min.

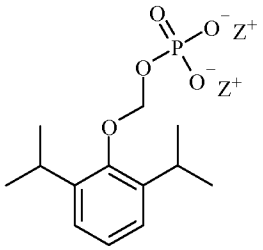
19. (withdrawn) The method of claim 18 wherein the compound is administered in an amount of from about 7 to about 15 mg/min.

20-35. (cancelled)

36. (rejected) The method of claim 12, wherein the compound is administered in an amount of from about 5 mg/kg to about 7.5 mg/kg.

37. (rejected) A method of producing a conscious sedated state in a human subject comprising administering to a human subject in need thereof a compound of Formula I:

Formula I



or a pharmaceutically acceptable salt thereof, wherein Z is alkali metal ion;

wherein the conscious sedated state is produced in the human subject by administering to the human subject at least one parenteral bolus injection in an amount of from about 5 mg/kg to about 10 mg/kg.

38. (rejected) The method of claim 37, wherein the compound is administered in an amount of from about 5 mg/kg to about 7.5 mg/kg.

39. (rejected) The method of claim 37, wherein the compound is O-phosphonooxymethyl propofol disodium salt.

IX. EVIDENCE APPENDIX

1. Declaration under 37 C.F.R. § 1.132 of Dr. Ajit Shah.

2. Diprivan® Product Insert.

X. RELATED PROCEEDINGS APPENDIX

NONE.